Comments on 1,3-Dioxolane
Robust Summary and Test Plans for the HPV Program

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On behalf of **Environmental Defense**

The Dioxolane Manufacturers' Consortium claim that the toxicological databases for 1,3-dioxolane are adequate and that no additional studies should be conducted. For the most part, this claim is correct with a couple of exceptions. First, one additional genetic toxicity test needs to be conducted and second information on biological half lives following different routes of exposure need to be provided. Detailed comments are itemized below.

1. Exposure- There is essentially no consumer exposure to 1,3-dioxolane although exposures in the work place could be as high as 1 ppm. Environmental exposures are low with levels in industrial wastewater ranging form non-detectable to 4ppm.

2. Acute Toxicity- 1,3-dioxolane exhibits low acute toxicity to rodents and various fish species and the existing database is adequate. We agree that not further acute toxicity tests should be conducted.

3. Repeat dose studies- The most sensitive toxicity endpoint is platelet number and effects on white blood cells. The liver, kidney and CNS also showed effects at high dose levels. The oral NOEL was 75 mg/kg/day and the inhalation NOEL was 500 ppm. These values are 2-3 orders of magnitude higher than worker exposures. We agree that no further repeat dose studies should be conducted

4) Subchronic studies- These studies are comprehensive and consistent with the repeat dose studies in that liver and the hematopoietic system exhibited toxic effects at high dose levels. The NOEL for inhalation was 300 ppm and 0.5 % in drinking water. Somewhat surprising was the reduction in serum cholinesterase at high doses. However this effect was less sensitive than the effect on blood cells.
We agree that no further subchronic studies are needed.

5). Genetic Toxicity- There is considerable information available on the genetic toxicity of 1,3-dioxolane in vitro and in vivo. Results are consistently negative in vitro for a variety of tests including the Ames test and chromosomal aberrations in CHO cells. However, some of the in vivo tests were positive. Of particular concern was the finding of single strand breaks in rat hepatocytes. The sponsor asserts that this finding is spurious. However, their justification for this claim is far from convincing. This test should be repeated using GLP. We also recommend that blood, liver and other samples from this test be archived for later evaluation using microarray technologies.

6) Sex related effects -No significant sex-related differences in toxicity were observed and

no further studies on sex differences and are needed

7. Reproduction/Development -Developmental effects were observed but only at maternally toxic doses. We agree that the studies on reproductive and developmental effects are complete and no further studies should be conducted.

8. Absorption, /Distribution/Metabolism- Some information is available but it is less than adequate. Studies should be conducted to determine the biological half-life in rodents following gavage, drinking water and inhalation exposures. This information is needed to evaluate possible risks from chronic exposures.

9. Lifetime Cancer Bioassay-Cancer bioassays have not been conducted and this raises some concern because of the blood cell effect seen in the repeat dose and subchronic studies. However, relatively high doses are required for these effects. The priority for a cancer bioassay, according to NTP standards, would fall between low and moderate.